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LETTER TO THE EDITOR

**SYSTEMIC NICKEL ALLERGY SYNDROME:
TIPS AND TRICKS ON HOW TO BE SUSPECTED AND TREATED**L. RICCIARDI¹, F. FURCI¹, S. ISOLA¹, P.L. MINCIULLO¹, S. SAITTA² and S. GANGEMI¹

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To the Editor,

Nickel is a metal among the most common contact allergens (1). Nickel allergic contact dermatitis (ACD) is not the exclusive phenotype of nickel sensitization as it is not only contained in metal objects but is also an essential nutrient in most foods. Nickel-induced clinical manifestations other than ACD include systemic contact dermatitis (SCD) and systemic nickel allergy syndrome (SNAS). SCD may occur in nickel sensitized individuals after ingesting nickel-containing foods, with a flare-up of earlier eczema lesions caused by previous exposure to the metal or in the form of pompholyx, vesicular hand eczema, baboon syndrome, papular macular exanthema, flexural eczema, itching, skin rash (2). SNAS is considered the association of gastrointestinal symptoms after ingestion of nickel-containing foods with cutaneous symptoms; gastrointestinal symptoms usually include bloating, diarrhea or constipation, vomiting, nausea, and abdominal pain (3).

Nickel-containing foods are mostly plant-derived foods. The nickel content of specific foods can vary widely, depending on the climate and season and the content in the soil or water. Foods recognized as particularly rich in nickel include peanuts, beans, lentils, peas, soybeans, oats, cocoa,

chocolate, nuts, whole wheat, pears and mushrooms (4). Gastrointestinal involvement in nickel allergic subjects has been reported by Di Gioacchino et al. (5) who described a marked inflammatory infiltrate of the duodenum mucosa in patients with nickel related ACD after an oral nickel challenge. Although there is no general concordance in literature on the efficacy of diet in nickel allergy, a low nickel specific diet called “BraMa-Ni” has been suggested for the work-up of the diagnosis of SNAS (6). Rizzi et al. studied the role of a low nickel diet in patients with irritable bowel syndrome (IBS) and nickel allergy, claiming that the almost complete avoidance of nickel sulfate with the adoption of a low nickel diet could explain the clinical benefits through a reduction of the pro-inflammatory state induced by nickel (7).

SNAS pathophysiology

SNAS pathophysiology involves both Th1 and Th2 cells; stimulation with nickel has been shown to induce specific patterns of cytokine secretion in lymphocyte cultures from metal-allergic patients, involving both Th1 and Th2-type cytokines (8).

Oxidative stress (OS) has also been reported to occur in patients who are diagnosed with SNAS as a consequence of the chronic inflammatory status

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Fig. 1. Cutaneous systemic reaction after Nickel oral provocation test with 1.25 mg of nickel sulfate.

provoked by systemic nickel sensitization. Signs of OS, such as higher serum levels of nitrosylated proteins (NPs), biomarkers of OS, were shown to be present in nickel-allergic patients affected by SNAS. These signs of OS are absent in patients with nickel ACD only (9).

Diagnostic work-up of SNAS: the nickel oral provocation test

SNAS can be suspected in subjects with Nickel ACD, positive to nickel patch-testing, with systemic cutaneous and gastrointestinal symptoms which improve after four weeks of low nickel diet (Table I). An Oral Nickel Provocation Test (OPT) is therefore conducted according to the following scheme: a dose of 1.25 mg of nickel sulfate (Lofarma S.p.A, Milan, Italy) is orally given on the first day in an open challenge fashion. After 24 h in the absence of symptoms another two single doses of 1.25 mg of nickel sulfate are given and the patient is evaluated the day after. The maximum cumulative dose of 3.75 mg of nickel sulphate was chosen on the basis of previous studies showing that this amount is approximately 10 times greater than the estimated normal daily dietary intake of nickel (10); usually SNAS patients react after a single dose of 1.25 mg.

The Nickel OPT is considered positive if cutaneous systemic symptoms occur with or without gastrointestinal symptoms. Typical cutaneous manifestations are flare-up of previous sites of contact dermatitis, flare-up reactions in previously positive nickel patch-test sites, itching or generalized erythema (Fig. 1). Typical gastrointestinal manifestations are bloating and diarrhea.

Nickel oral hyposensitizing treatment

Nickel desensitization can be proposed for the treatment of SNAS in patients with a compromised quality of life. Nickel oral hyposensitizing treatment (NiOHT) (Lofarma, Milan, Italy) consists in the administration of an up-dosing of nickel sulfate from 1 ng to 10, 100 and up to 500 ng. Oral nickel doses are taken three times per week and the maintenance dose of 500 ng is reached in 4 weeks and, in our experience, continued up to 2-3 years. A one-year double-blind, randomized, placebo-controlled trial evaluating the efficacy of NiOHT in patients with SNAS was carried out on patients from different Allergy centers in Italy (11). The study concluded that NiOHT is effective in SNAS, in particular, on gastrointestinal manifestations, but also on cutaneous symptoms, and allows patients with SNAS to safely

Table I. *Low nickel diet: food allowed and food not allowed.*

Food allowed		Food not allowed	
SPICE AND DRESSING	Paprika, pepper, olive oil, vinegar, mayonnaise, tomato sauce, salt.	VEGETABLES	Asparagus, broccoli, artichokes, carrots, cabbage, cauliflower, onions, green beans, peas, fennel, mushrooms, lettuce, tomatoes, rocket salad, celery, spinach, Brussels sprouts.
DRINKS	Frozen drinks, beer (not canned), coffee, wine.	FRUIT	Apricots, pineapples, watermelon, avocado, cherries, figs, berries, kiwi, pears, plums, grapes.
CEREALS	Plain flour, bread, pasta, pizza, rice.	HERBS AND DRESSING	Bay leaves, basil, parsley, ketchup, seed oil, mustard.
VEGETABLE AND FRUITS	Citrus fruits, bananas, apples, melons, peaches, cucumbers, aubergines, peppers, potatoes, garlic, pumpkins, courgettes.	CEREALS	Wholemeal products, buckwheat oat, barley, maize, malt, rye, soy.
FISH	Sword-fish, tuna.	SEAFOOD	Cod, shell-fish, salmon, octopus, squid, plaice.
SWEETS	Choux-pastry, biscuits, custard, honey, pastry, sponge cakes, sugar.	CHOCOLATE	All chocolate sweets.
OTHERS	Meat, eggs, salami, ham, dairy products.	NUTS	All of them
		DRINKS	Tea

re-introduce Ni-rich foods, improving their quality of life.

Tolerance to nickel has been reported to be associated with the increase of T regulatory cells. A two-year treatment with NiOHT induced a significant reduction of serum IL-2 levels while IL-10 levels increased (12). The interplaying balance between the two cytokines, IL-2 and IL-10, induced by oral tolerance to NiOHT, is supposed to have an important role in provoking anergy in T cells responsible for SNAS.

CONCLUSIONS

Although, the presence of nickel in foods is nowadays well known, the possibility of SNAS occurring is still greatly debated; the mechanism

inducing a systemic reaction only in a subset of Ni-ACD patients is yet to be understood. Information on how to clinically suspect SNAS and which is the correct diagnostic and treatment management is of great interest not only for allergists but also for dermatologists and internists as well as for nutritionists and dieticians.

NiOHT is the only current available treatment for SNAS which can restore the immunoregulatory mechanisms altered by nickel systemic sensitization.

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